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Our File No. GEN01-003-CON-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Mary E. Gerritsen, et al.

Serial No. 09/865,859

Filing Date: May 25, 2001

Examiner Sabiha Naim Qazi

Group Art Unit No. 1616

For Method of Inhibiting Angiogenesis

RESUBMISSION OF APPEAL BRIEF FILED ON MARCH 11, 2004

M.S. - Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Examiner Qazi notified Applicant that the Appellants' Brief on Appeal had not been matched up with the file. Applicants have enclosed a copy of the following documents originally filed, via first class mailing certificate on March 11, 2004:

1. Postcard
2. Credit Card Payment Form
3. Transmittal of Appellants' Brief On Appeal (in duplicate)
4. Petition for a Five Month Extension of Time (in duplicate)
5. Appellant's Brief on Appeal (in triplicate)

Respectfully submitted,

Paul E. Rauch, Ph.D.
Registration No. 38,591
Attorney for Applicant

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Chicago, Illinois 60661
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Case No.	**09800080-0035**
Applicant:	**Mary E. Gerritsen, et al.**
Serial No.	[redacted] 09/865,459
Filing Date:	**May 25, 2001**
For:	**Method of Inhibiting Angiogenesis**

Mail Stop - Appeal Brief-Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Transmitted herewith is:

- ☒ 2 Credit Card Forms
- ☒ Transmittal Of Appellants' Brief On Appeal (in duplicate)
- ☒ Petition for a Five Month Extension of Time (in duplicate)
- ☒ Appellants' Brief On Appeal (in triplicate)

Date of Mailing

Paul E. Rauch, Ph.D., Registration No. 38,591
March 11, 2004

Attorney Docket No. 09800080-0035

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of	)	Group Art Unit 1616
	)	
Mary E. Gerritsen *et al.*	)	Examiner: Sabiha Naim Qazi
Application No. [redacted] 09/865,859	)	
Filed: 25 May 2001	)	
For: Method of Inhibiting Angiogenesis	)	

I hereby certify that this document is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on March 11, 2004.

Commissioner for Patents
Alexandria, VA 22313-1450

TRANSMITTAL OF APPELLANTS' BRIEF ON APPEAL

Dear Sir:

Appellants submit, in triplicate, Appellants' Brief on Appeal under 37 C.F.R. § 1.192 in support of the Notice of Appeal filed on 08 August 2003. Appellants also submit a check in the amount of $330 for the appeal fee as required by 37 C.F.R. § 1.17(c).

The Commissioner is hereby authorized to credit overpayments or to charge any deficiency in a required fee to Deposit Account No. 19-3140. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Dated: March 11, 2004 By: _____
Paul E. Rauch, Ph.D. Reg. No. 38,591

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Attorney Docket No. 09800080-0035 (Formally 10466/32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of	Group Art Unit 1616
Mary E. Gerritsen *et al.*	Examiner: Sabiha Naim Qazi
Application No. [redacted] 09/865,859	I hereby certify that this document is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on March 11, 2004.
Filed: 25 May 2001	
For: Method of Inhibiting Angiogenesis	

Commissioner for Patents
Alexandria, VA 22313-1450

APPELLANTS' BRIEF ON APPEAL

Dear Sir:

In accordance with the provisions of 37 C.F.R. § 1.192, Appellants submit this Brief in support of the Appeal for the above-referenced application.

I. REAL PARTY IN INTEREST

The real party in interest in the present appeal is the Assignee, Genentech, Inc., a U.S. corporation. The Assignment was recorded in the U.S. Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals and no related interferences.

III. STATUS OF CLAIMS

Claims 1-18 are pending in this appeal, of which claims 1 and 12 are independent. Claims 19-29 were canceled. Claims 1-18 are appealed.

IV. STATUS OF AMENDMENTS

An Amendment After Final was filed on 11 July 2003. An Advisory Action was mailed 28 July 2003, which was unclear about entry of the Amendment After Final, because no box was marked to indicate entry or no entry, one reason for not entering the amendment was marked, and the comments by the Examiner referred to new claims introduced by the amendment. Via telephone on Friday February 6, 2004, the Examiner confirmed that the Amendment After Final was not entered.

V. SUMMARY OF INVENTION

The present invention relates to a method of inhibiting angiogenesis. Angiogenesis is the developmental process whereby new blood vessels are formed from endothelial cells (the cells which line blood vessels). Angiogenesis is essential to a variety of normal and pathological conditions, including organ development, wound healing, and tumor growth and metastasis (page 3, lines 18-20). Endothelial cells differentiate into endothelial cell tube-like structures that are precursor structures to blood vessel formation (page 9, lines 15-16).

The present invention is based on the discovery that PPAR gamma is a protein that is expressed in endothelial cells and, when activated by a ligand, is a potent inhibitor of endothelial cell differentiation (page 9, lines 10-14). The claimed invention is a method of inhibiting angiogenesis, and includes administering a PPAR gamma ligand, wherein angiogenesis is

inhibited. Furthermore, administration of a PPAR gamma ligand and a retinoic acid (RXR) receptor ligand results in synergistic inhibition of angiogenesis (page 10, lines 3-7).

VI. ISSUE

The issue on Appeal is as follows: Whether claims 1-18 are properly rejected under section 103(a) over Urban *et al.* (5,814,647) in view of Cushman *et al.* (J. Med. Chem. (1997) Vol. 40, No. 15, 2323-2334).

VII. GROUPING OF CLAIMS

The claims do not stand or fall together. Specific arguments as to the separate patentability of the claims have been presented.

VIII. ARGUMENT

The Examiner has pointed out that Urban *et al.* describe use of thiazolidinedione compounds as PPAR gamma ligands in the treatment of cancer, and that Cushman *et al.* defines angiogenesis as the formation of new blood vessels required for the growth of solid tumors. The Examiner has leaped to the incorrect conclusion that compounds that are useful for treating cancer do so only through inhibiting angiogenesis, and improperly reached the conclusion that Urban *et al.* in combination with Cushman *et al.* suggest that PPAR gamma ligands inhibit angiogenesis. Furthermore, the examiner has completely ignored claim element (a), which specifies identifying a patient in need of an angiogenesis inhibitor (claim 1 and claims dependent thereon); or which specifies identifying a patient with a disease or disorder susceptible to angiogenesis inhibition (claim 12, and claims dependent thereon).

Some strategies for treating cancer rely on the fact that cancer cells are fast growing, unlike most cells in the human body. By administering a compound that is directly toxic to the cancer cells, the hope is that these fast growing cancer cells will be poisoned and killed before the toxic compound adversely compromises the overall health of the patient. It is this toxicity that results in many of the well known side effects of chemotherapy: hair loss, organ failure, anemia and immunosuppression.

In the case of tumor forming cancers, another strategy is possible -- inhibiting the formation of blood vessels necessary for the growth of tumors. The formation of blood vessels, known as angiogenesis, into a tumor is necessary as the tumor grows large to provide nutrients and oxygen to all cancer cells in the tumor. This strategy indirectly attacks the cancer cells: endothelial cells are the targets of angiogenesis inhibition, and by disrupting their organized formation into blood vessels, tumors are prevented from growing, new tumors cannot form, and in the case of very rapidly growing tumors, the cells will die when their demand for nutrients and oxygen outstrips the supply. There are other diseases that may also be treated by inhibiting angiogenesis, such as rheumatoid arthritis, psoriasis and neovascular glaucoma.

A. The applied art

Urban *et al.* describe PPAR gamma ligands for the treatment of climacteric symptoms. These compounds are described as inhibiting steroidogenesis in granulosa cells, and that troglitazone can directly kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPAR gamma, while not affecting the viability of normal cells (column 2, lines 65 - column 3, line 5). The examples describe treating cell lines with troglitazone; no actual tumors or patients having cancer are treated. Examples 7 and 8 are prophetic, and were not actually carried out. There is no description or suggestion of the inhibition of angiogenesis, or in any

way affecting endothelial cells or blood vessel formation. Furthermore, there is no description or suggestion of identifying patients in need of an angiogenesis inhibitor. Urban *et al*, therefore, does not disclose inhibiting angiogenesis and does not disclose the claimed invention.

Cushman *et al.* describe that angiogenesis is the formation of new blood vessels; there is no suggestion that troglitazone or PPAR gamma ligands inhibit angiogenesis. Furthermore, there is no description or suggestion of identifying patients in need of an angiogenesis inhibitor. Cushman *et al* does not overcome the deficiencies of Urban *et al* since neither reference teaches inhibiting angiogenesis with a PPAR gamma ligand.

B. The Examiner's rejection

In the office action (Office Action mailed 2/11/2003 (paper no. 12)), the Examiner has pointed out that Urban *et al.* teach the use of troglitazone and related thiazolidinedione compounds as PPAR gamma ligands in the treatment of cancer (see Urban *et al.*, lines 1-5 and 13-22, col. 3; examples 5 and 6). Then, noting that Urban *et al.* do not teach "angiogenesis," *per se*, the examiner points out that Cushman *et al.* teach "angiogenesis" as the formation of new blood vessels required for the growth of solid tumors (lines 16-23, col. 1; page 2323). The Examiner concludes that since Urban *et al.* teach that troglitazone (a PPAR gamma ligand) may be used for the treatment of cancer, then it also must teach that these compounds are useful for the inhibition of angiogenesis. As motivation, the Examiner states: "it would have been obvious to one skilled in the art at the time of invention to be motivated to use troglitazone for treatment of cancer and for inhibition of angiogenesis because angiogenesis is the formation of new blood vessels." The Examiner confirmed this position in an Advisory Action (mailed 28 July 2003 (paper no. 16)).

C. Applicant's Argument Against the Rejection

The references Urban *et al* and Cushman *et al* do not suggest nor render the claimed invention obvious under 35 USC 103 because the references alone, or when considered together, do not disclose or suggest (a) identifying a patient in need of an angiogenesis inhibitor or (b) administering a PPAR gamma ligand to such patient to inhibit angiogenesis. The Examiner has not established a prima facie case of obviousness based on the combined disclosures of Urban *et al* and Cushman *et al*. Since a prima facie case of obviousness has not been established, withdrawal or reversal of this rejection is respectfully requested.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. (M.P.E.P. 2143 "Basic Requirements of a *Prima Facie* Case of Obviousness" citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art; all words in a claim must be considered in judging the patentability of that claim against the prior art. (M.P.E.P. 2143.03 "All Claim Limitations Must Be Taught or Suggested", citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). and *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)).

The Examiner has not established that the references teach or suggest claim element (a) of independent claims 1 and 12, that is, identifying a patient in need of an angiogenesis inhibitor

(claim 1, and claims dependent thereon); or identifying a patient with a disease or disorder susceptible to angiogenesis inhibition (claim 12, and claims dependent thereon). The references alone or in combination do not suggest element (a) of the claims. The examiner has not sustained the burden of establishing a prima facie case with respect to this element of the claims.

The prior art cited by the Examiner is also silent about the effect of PPAR gamma ligands on angiogenesis or even that PPAR gamma is expressed on endothelial cells. Urban *et al.* teach something different -- that PPAR gamma ligands can directly kill transformed or cancer cells that express PPAR gamma (Urban *et al.*, column 23, lines 2-5 and 60-61). Urban *et al.* state in the Abstract " enhanced translocation of this orphan receptor [PPAR gamma] into the nucleus of cells will block transcription in rapidly proliferating cancer cells that express PPAR gamma, resulting in loss of cell viability." This reference teaches direct killing of cancer cells expressing PPAR gamma and does not teach or suggest that epithelial cells express PPAR gamma or that angiogenesis can be inhibited using a PPAR gamma ligand. Urban *et al* would lead one away from the claimed invention.

The claimed invention is a method of inhibiting angiogenesis. As part of this method, a PPAR gamma ligand is administered, and angiogenesis is inhibited (claim element (b)). Urban *et al.* fail to describe or suggest inhibiting angiogenesis, or any effect on endothelial cells. Urban *et al.* never even consider the inhibition of angiogenesis: all actual experiments were conducted on individual cells, so there were no tumors nor blood vessels which could have been examined for this effect. In fact, Urban *et al.* reached an entirely different conclusion, that PPAR gamma ligands attack certain cancers by directly killing these specific cancer cells. Cushman *et al.* have only been cited for the definition of angiogenesis. Accordingly, Applicants submit that there is no description or suggestion in the applied references to inhibit angiogenesis with troglitazone or any PPAR gamma ligand. The references alone or in combination do not suggest element (b) of

the claims. The examiner has also not sustained the burden of establishing a prima facie case with respect to this element of the claims.

Since a prima facie case of obviousness has not been established for either element (a) or element (b) of the claims, the Examiner has not established that the claims as a whole are obvious over the prior art of record.

D. Specific arguments as to the separate patentability of selected claims

For each claim beyond claim 1, Applicants provide specific arguments as to their separate patentability.

Concerning claims 2, 3, 13 and 14, no reference teaches that PPAR gamma ligands inhibit angiogenesis in a mammal or a human.

Concerning claim 4, the references fail to teach or suggest administering an angiogenesis inhibiting amount of a PPAR gamma ligand.

Concerning claims 5 and 15, the references fail to teach or suggest administering a therapeutically effective amount of a RXR receptor ligand and a PPAR gamma ligand. Furthermore, the application states that when used together, a RXR receptor ligand and a PPAR gamma ligand provide a synergistic effect on angiogenesis. These results provide further evidence of unobviousness.

Concerning claims 6, 7, 8, 16, 17 and 18, the references fail to teach or suggest that the specifically listed PPAR gamma ligands inhibit angiogenesis.

Concerning claim 9, the references fail to teach or suggest a patient that has a disease or disorder characterized by undesirable excessive neovascularization.

Concerning claims 10 and 12, the references fail to teach or suggest that angiogenesis may be inhibited by a PPAR gamma ligand in patients that have the specifically listed diseasse or disorders.

Concerning claim 11, the references fail to teach or suggest that a PPAR gamma ligand may inhibit angiogenesis in a solid malignant tumor.

IX. Conclusion

Applicants respectfully submit that the outstanding rejections should be reversed, and that the application is in condition for allowance.

Respectfully submitted,

Dated: March 11, 2004 By: _____

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